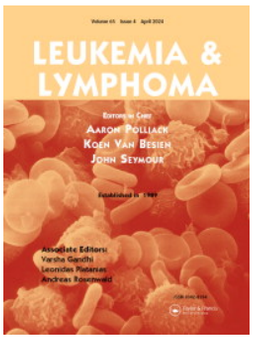

Taylor & Francis
Taylor & Francis Group

Leukemia & Lymphoma

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ilal20

Lymphoplasmacytic lymphoma and multiple myeloma coexisting in the same patient: a case series and literature review

Gilad Itchaki, Osnat Jarhovsky, Jorge J. Castillo, Hamza Hassan, Moshe L. Gatt, Merav Leiba, Pia Raanani, Morie A. Gertz & Iuliana Vaxman

To cite this article: Gilad Itchaki, Osnat Jarhovsky, Jorge J. Castillo, Hamza Hassan, Moshe L. Gatt, Merav Leiba, Pia Raanani, Morie A. Gertz & Iuliana Vaxman (19 Mar 2024): Lymphoplasmacytic lymphoma and multiple myeloma coexisting in the same patient: a case series and literature review, Leukemia & Lymphoma, DOI: 10.1080/10428194.2024.2332499

To link to this article: https://doi.org/10.1080/10428194.2024.2332499

Published online: 19 Mar 2024.

LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2024.2332499

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Lymphoplasmacytic lymphoma and multiple myeloma coexisting in the same patient: a case series and literature review

Gilad Itchaki[a,b], Osnat Jarhovsky[a,b], Jorge J. Castillo[c], Hamza Hassan[c], Moshe L. Gatt[d], Merav Leiba[e], Pia Raanani[a,f], Morie A. Gertz[g] and Iuliana Vaxman[a,f,g]

[a]Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; [b]Hematology, Meir Medical Center, Kfar-Saba, Israel; [c]Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA; [d]Department of Hematology, Hadassah Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel; [e]Assuta Ashdod University Hospital, Faculty of Health Science, Ben-Gurion University of the Negev, Negev, Israel; [f]Institute of Hematology, Davidoff Cancer Center, Rabin Medical Center, Petah Tikvah, Israel; [g]Division of Hematology, Mayo Clinic, Rochester, Minnesota, USA

ABSTRACT

The simultaneous occurrence of Waldenström macroglobulinemia and multiple myeloma in the same patient has been published as case reports. Patients with Waldenström macroglobulinemia often have a small clone of plasma cells. However, the concurrent occurrence of symptomatic myeloma with lytic bone lesions is rare. The diagnosis of this 'hybrid' entity is challenging, and there are no standard therapies. We present six patients from five centers (three in Israel and two in the United States). We describe these patients' unique clinical course and treatment approaches.

ARTICLE HISTORY
Received 31 December 2023
Revised 29 February 2024
Accepted 13 March 2024

KEYWORDS
Myeloma; Waldenström macroglobulinemia; plasma cell dyscrasia

Introduction

Multiple myeloma (MM) and Waldenström macroglobulinemia (WM) are two mature B-cell neoplasms [1]. The association of multiple myeloma with another B-cell lymphoproliferative disease has been previously reported, most commonly the simultaneous occurrence of multiple myeloma and chronic lymphocytic leukemia (CLL) [2]. The association with MALT lymphoma, follicular lymphoma, and mantle cell lymphoma is also well recognized [3].

Waldenström macroglobulinemia is a rare B-cell lymphoproliferative disease, representing 2% of non-Hodgkin's lymphomas [4]. It is characterized by an IgM monoclonal protein and an excess of neoplastic lymphocytes, plasmacytoid cells, and plasma cells in the bone marrow and other organs. There is no specific diagnostic immunophenotypic or cytogenetic abnormality in Waldenström macroglobulinemia. Deletion of the long arm of chromosome 6 (6q-) occurs in more than 40% of Waldenström macroglobulinemia cases [5]. In 2012, a MYD88 L265P somatic mutation was described in 91% of Waldenström macroglobulinemia patients [6]. MYD88 L265P, which is very sensitive for Waldenström macroglobulinemia, is present in 6–20% of splenic marginal zone lymphomas [7, 8] and 3% of CLL patients [9]. In contrast, multiple myeloma, including IgM myeloma, is always negative for MYD88 L265P mutation. In a study that included 924 Waldenström macroglobulinemia patients, 17 patients (2.8%) had a second hematologic malignancy (13 diffuse large B cell lymphoma (DLBCL) and 4 acute myeloid leukemia (AML) [10].

The coexistence of Waldenström macroglobulinemia and multiple myeloma is exceedingly rare and has been previously reported only as individual case reports [11–15]. The diagnosis can be challenging because of the morphologic similarities between multiple myeloma and Waldenström macroglobulinemia.

We describe concurrent Waldenström macroglobulinemia and multiple myeloma and discuss the approach to these patients.

Methods

We reviewed the hospital records of six patients who had both multiple myeloma and Waldenström macroglobulinemia. The study was approved by the institutional review board of the 5 participating centers per the principles of the Helsinki Declaration. The first patient was diagnosed and treated in the Institute of

CONTACT Iuliana Vaxman sjuliava@gmail.com Institute of Hematology, Davidoff Cancer Center, Rabin Medical Center, Petah Tikvah, Israel

Hematology at the Davidoff Cancer Center, Rabin Medical Center in Israel, and patients 2–3 were diagnosed and treated at Meir Medical Center in Israel. Patient 4 was diagnosed and treated at Assuta Medical Center, Israel. Patient 5 was diagnosed and treated at the Mayo Clinic, Rochester, MN, USA, and patient 6 was diagnosed at the Dana-Farber Cancer Institute, Boston, MA, USA.

Case presentations

Patient 1

An 83-year-old woman, presented in March 2021 with mild anemia. She had two monoclonal proteins in the serum: an IgG kappa of 5.4 g/dL and an IgM kappa of 0.8 g/dL. At presentation her hemoglobin was 11 g/dL, creatinine was 1.1 mg/dL, and light chain protein in the urine was detected without albumin. Bone marrow biopsy demonstrated 70% lymphoplasmacytic cells (LP) and 20% monoclonal plasma cells. MYD88 L265P was positive by next-generation sequencing (NGS). Her PET/CT scan was negative for lytic bone lesions and lymphadenopathy. The patient was diagnosed as smoldering WM (SMW) and monitored until July 2022 when her hemoglobin decreased to 8 g/dL.

At that point, there was no evidence of hemolysis or nutrient deficiency and cryoglobulins were negative. PET/CT demonstrated multiple new lytic lesions in the vertebrae, sternum, pelvis, and ribs, without lymphadenopathy or splenomegaly. IgG levels rose from 4090 mg/dL to 7380 mg/dL and total IgM decreased from 1265 mg/dL to 836 mg/dL. The IgG kappa protein rose from 5.4 g/dL to 6.4 g/dL and an IgM kappa protein of 0.8 g/dL decreased to 0.6 g/dL. A repeat bone marrow biopsy showed 30% lymphoplasmacytic cells (CD20+ CD79a + BCL2+ PAX5+ CD10- CD5- BCL6-). In addition, there was an increased number of monoclonal plasma cells (CD138+ CD20-) kappa light chain restricted occupying 50% of the specimen. Comparing this bone marrow biopsy to the previous one, the number of plasma cells increased while the number of lymphoplasmacytic cells significantly decreased. FISH testing, done on sorted cells, showed a 1q21 gain in 89% of the plasma cells.

Treatment with VCd (bortezomib 1.3 mg/m^2 once weekly, cyclophosphamide 500 mg once weekly, and dexamethasone 20 mg once weekly) was initiated. Her hemoglobin normalized after 2 cycles of VCd, IgG normalized, and IgM levels decreased by 50% after 4 cycles of VCd compatible with a very good partial response (VGPR) to multiple myeloma and a partial response (PR) to Waldenström macroglobulinemia.

Patient 2

A 63-year-old male was diagnosed in 2013 with indolent B-cell lymphoma (CD5+ CD20 + CD38-) through a bone marrow biopsy. The monoclonal protein level was IgA kappa 6 g/dL, hemoglobin was 13.5 g/dL. The patient was monitored until March 2021 when he presented with bilateral retinal vein occlusion and hemoglobin of 4.7 g/dL. A physical exam showed enlarged lymph nodes in his left axilla and groin, and his spleen was palpated 4 cm below the left costal margin. At this time, the platelet level was 14000/μL, and neutrophils were 1100/μL. Total protein was 9.7 g/dL with albumin 2.7 g/dL, creatinine, calcium, and LDH levels were within normal limits, and serum IgA level was 5470 mg/dL with a reciprocal reduction of IgG and IgM levels. Bone marrow biopsy demonstrated 70% infiltration by lymphoplasmacytic cells, positive for CD20 with kappa monoclonality and another smaller population of plasma cells (30%). Myeloma FISH panel, done on sorted plasma cells, was normal, and MYD88 L265P was detected by PCR. PET-CT demonstrated an enlarged spleen of 17 cm and enlarged abdominal lymph nodes (the largest one of 5.6 cm) with low FDG uptake of 4 and multiple lytic bone lesions.

The working diagnosis was IgA-associated lymphoplasmacytic lymphoma (LPL) and the patient received 6 cycles of bendamustine and rituximab (BR) and IgA levels decreased from 6200 mg/dL to 3000 mg/dL with an increase in hemoglobin level from 4.5 to 10 g/dL and platelet levels rose from 14000/μL to 55000/μL. PET/CT scan after 6 cycles of BR showed normal spleen size and no lymphadenopathy, lytic lesions were unchanged with persistent high FDG uptake. The patient underwent a bone biopsy of a lytic lesion that showed 100% infiltration by plasma cells. Therefore, after completing 6 BR cycles the patient started treatment with VRd (bortezomib 1.3 mg/m2 once weekly, lenalidomide 25 mg/d, dexamethasone 20 mg once weekly). After one cycle, lenalidomide was discontinued due to thrombocytopenia and treatment with daratumumab, bortezomib, dexamethasone (DVd) was initiated. An attempt at stem cell mobilization after 2 DVd cycles failed. Nonetheless, hemoglobin improved to 13.5 g/dL and IgA decreased to 1400 g/dL. After 8 DVD cycles, treatment was discontinued, and the patient maintained the response.

Patient 3

A 75-year-old male presented with an elevated total protein of 8 g/dL, hemoglobin level of 10 g/dL, and an IgM level of 6600 mg/dL. As part of the evaluation, he

underwent a CT scan that showed generalized mild lymphadenopathy. A bone marrow biopsy demonstrated 30% lymphoplasmacytic cells and 30% plasma cells. MYD 88 L265P was not detected. He was lost to follow-up for two years when he presented with retinal bleeding, gastrointestinal bleeding, hematuria, and bloody pleural effusion. Hemoglobin was 4.9 g/dL, and his IgM level was 8900 mg/dL, monoclonal protein level was 7.5 g/dL. He was diagnosed with an acquired von-Willebrand factor (vWF) deficiency secondary to plasma cell dyscrasia. Bone marrow biopsy showed a significant rise in plasma cells comprising 70% of marrow cellularity and 20% lymphoplasmacytic cells. Since the patient was MYD 88 L265P negative and had 70% plasma cells in the bone marrow, the patient was treated as MM. He started VCd, active in both Waldenström macroglobulinemia and multiple myeloma, with no change in IgM levels or symptoms after the first cycle, and therapy was switched to BR. After 2 cycles, IgM levels decreased to 6720 mg/dL and hemoglobin levels rose to 10 g/dL. A new supraclavicular lymph node appeared at that point, and a biopsy demonstrated a transformation to DLBCL. Treatment with rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone (R-CHOP) was initiated. The patient did not respond to therapy and died 5 months later from progressive DLBCL.

Patient 4

A 75-year-old male, presented in 2014 with lumbar back pain and IgM kappa monoclonal protein of 3 g/dL, creatinine of 2.2 mg/dL, and hemoglobin of 8 mg/dL. Bone marrow biopsy showed 50% lymphoplasmacytic cells, and FISH was without any abnormality (FISH was done on unsorted cells since cell sorting techniques were unavailable in 2014). Total body low-dose CT showed degenerative changes in the spine without lytic lesions. With the working diagnosis of Waldenström macroglobulinemia, the patient was treated with RCd (rituximab, cyclophosphamide, and dexamethasone) with no response. Two months after treatment was initiated, creatinine levels rose quickly from 2.2 to 7 mg/dL and hemodialysis was started. A renal biopsy demonstrated infiltration of the kidney with plasma cells without cast nephropathy. Due to the rapid creatinine rise and the large number of plasma cells infiltrating the kidney, treatment was switched to VCd and after 2 cycles creatinine decreased to 2.7 mg/dL with no monoclonal protein. After a year of VCd, free light chain (FLC) kappa started to rise from normal to 40 mg/dL and treatment was changed from VCd to lenalidomide and dexamethasone (Rd). The patient achieved a very good partial response (VGPR). In 2018 the patient was hospitalized several times due to episodes of sepsis and hemodialysis was initiated. The patient continued lenalidomide maintenance and maintained a response for 7 years.

Patient 5

A 72-year-old female, presented in 2010 with mild anemia of 11 g/dL. Evaluation demonstrated two monoclonal proteins: IgM kappa of 0.9 g/dL, and IgG kappa of 3.1 gr/dL. Bone marrow biopsy demonstrated 20% plasma cells and 30% lymphoplasmacytic cells. FISH analysis showed no aberrations. The patient was diagnosed with smoldering MM and Waldenström macroglobulinemia. After 5 months, hemoglobin levels decreased to 9.5 g/dL, monoclonal proteins rose by 10% to IgM kappa 1 gr/dL and IgG kappa 3.4 gr/L, and bone marrow biopsy showed 50% lymphoplasmacytic cells with focal clusters of plasma cells. WBC levels rose to 13800/μL with 11800/ μL lymphocytes. Treatment with RCd was initiated with minimal hemoglobin rise after 2 cycles, and treatment was switched to RVd (rituximab, bortezomib, and dexamethasone). Response was achieved with hemoglobin rise to 11 g/dL and IgM level decrease by 50% but IgG levels rose from 4210 mg/dL to 5150 mg/dL. Therapy was complicated by pneumocystis jiroveci pneumonia (PJP). She completed 6 cycles of RVd. After 4 years, hemoglobin levels progressively declined to 9.5 g/dL, IgM kappa levels rose to 5 g/dL, IgG kappa remained stable at 0.5 g/dL, and bone marrow showed 50% LP and MYD88 L265P was detected. In 2019, the patient was treated with three cycles of BR which was discontinued due to COVID-19 infection. Treatment was not resumed since hemoglobin was stable and the patient was asymptomatic. At the end of follow-up 5 years later, she is still in remission.

Patient 6

A 71-year-old female with a known history of JAK2 positive polycythemia vera (PV) treated with hydroxyurea and known IgG lambda monoclonal gammopathy of undetermined significance (MGUS) presented in March 2020 with worsening macrocytic anemia of 10.6 g/dL. Bone marrow biopsy was suggestive of early post-PV fibrosis with no increased blast percentage. Also noted were 30% lambda-restricted plasma cells (with aberrant CD20 expression) and a 40% monoclonal IgM kappa-restricted B-cell clone with lymphoplasmacytic differentiation (CD19/CD20/CD22/PAX-5/IgM

positive, CD5/CD10 negative). PET-CT did not show any FDG avid lytic lesions, lymphadenopathy or splenomegaly. Serum IgM levels were within normal limits (200 mg/dL), and hydroxyurea was discontinued with hemoglobin normalization. The patient was followed as smoldering multiple myeloma. In March 2022, the patient presented with worsening fatigue and recurrent macrocytic anemia with hemoglobin of 8.7 g/dL with no evidence of hemolysis. Repeat bone marrow evaluation showed persistent 2–3+ fibrosis along with increased lambda-restricted plasma cells comprising 80% of marrow cellularity in addition to a lymphoplasmacytic Kappa clone consisting of only 10% marrow involvement. MYD88 L265P mutation was detected. Immunohistoechemical stains were positive for CD56 and cyclin D1 on plasma cells and bone marrow FISH demonstrated t(4;14) rearrangement and monosomy 13. IgG lambda was 5.6 g/dL with low-level IgM kappa monoclonal protein and IgM level of only 99 mg/dL. Serum kappa and lambda FLC were 4.2 and 1.7 mg/dL, respectively. A repeat PET-CT scan showed multiple PET avid lytic lesions and the patient was diagnosed as revised international staging system (RISS) Stage II IgG lambda multiple myeloma along with IgM Kappa MYD88 L265P mutated Waldenström macroglobulinemia. The patient was treated with 6 cycles of DVRd that led to the resolution of anemia and hematologic CR for myeloma. A repeat bone marrow showed undetectable minimal residual disease (MRD) for the IgG Lambda clone at 10^{-6} by NGS. However, she still has persistent involvement with 5% kappa-restricted lymphoplasmacytic lymphocytes. Autologous stem cell transplant was deferred due to her history of post-PV fibrosis and risk of poor engraftment and negative MRD. At present, 14 months after diagnosis, the patient is asymptomatic and in remission maintained on bortezomib/lenalidomide due to high-risk cytogenetics.

Discussion

This is the first case series of Waldenström macroglobulinemia/LPL and multiple myeloma simultaneous occurrence. We describe six cases with various presentations and management strategies. These cases are difficult to diagnose, and no standardized management approach exists.

The coexistence of Waldenström macroglobulinemia and multiple myeloma in the same patient is extremely rare and has been previously reported only in five case reports [11–15]. Ours is the first case series describing this co-occurrence. In the present case series, three patients (50%) were males, and the median age was 72 years. The presenting symptoms were nonspecific (fatigue, weakness, weight loss) in 6 patients, lymphadenopathy and hepatosplenomegaly in 1 patient, and hyperviscosity in 2 patients. Anemia was present in all patients at diagnosis and was the only treatment indication in 3. Three patients had lytic bone lesions. This entity is commonly, but not necessarily, associated with biclonal monoclonal proteins. Five patients had a monoclonal IgM protein, 3 had a monoclonal IgG protein. Four patients had MYD88 L265P positive disease, 1 had MYD88 wildtype disease, and the mutation was not evaluated in one patient. Translocation t(11;14) was tested in all patients and was present in none. Table 1 shows the characteristics of all six patients. None of the patients had features compatible with light-chain amyloidosis.

The clinical courses and laboratory findings of patients 1, 4, and 6and the results of the laboratory studies resemble multiple myeloma more closely than Waldenström macroglobulinemia, while the clinical features of patients 2, 3, and 5 are more consistent with Waldenström macroglobulinemia. The serum concentration of IgG/IgA *vs.* IgM cannot be used to determine whether the patient has symptoms due to Waldenström macroglobulinemia or multiple myeloma. In some of the patients, particularly in patient 5, IgG/IgA levels were much higher than IgM, but the patient's symptoms, and extent of marrow infiltration, were compatible with Waldenström macroglobulinemia rather than multiple myeloma. Patient 6 is the only patient with different restriction of light chains (plasma cell clone restricted to lambda and Waldenström macroglobulinemia clone restricted to kappa). There is only one similar previous case report, published in 1981 [13]. Patient 2 is the only patient described in the literature with no IGM LPL with lytic lesions.

The simultaneous presentation of Waldenström macroglobulinemia and multiple myeloma has been reported in 5 case reports. Table 2 summarizes these cases. MYD88 was positive only in one case, and all others were reported before the introduction of the MYD88 test. The diagnostic challenge arises from the fact that a small population of clonal plasma cells is often detected in Waldenström macroglobulinemia. Our case series is unique since through the routine use of FISH and MYD88 L265P, we were able to better establish the diagnosis. The entity of simultaneous Waldenström macroglobulinemia and multiple myeloma poses a diagnostic challenge and underlines the importance of testing for MYD88 L265P. The MYD88 L265P mutation is a sensitive and specific molecular abnormality in LPL. The main differential of Waldenström macroglobulinemia includes marginal zone lymphoma with plasmacytic differentiation and

Table 1. Patients' characteristics.

Pt Number	Age/ Gender	Paraprotein	Bone Marrow	FISH	MYD88 L265Pmutation	Therapy indication	Treatment and outcome
1	83/F	IgGk IgMk	WM 30% MM 50%	1q21 gain in 89% of the plasma cells	Yes	Anemia, lytic lesions in the vertebras, sternum, pelvis, and ribs	VCd- hemoglobin normalized after 2 cycles of VCd, IgG normalized, and IgM decreased by 50% after 4 cycles of VCd. MM response- VGPR
2	63/M	IgAk	LPL 90% MM-10%	Normal	Yes	Bilateral retinal vein occlusion and hemoglobin 4 g/dL, lymphadenopathy, splenomegaly, multiple lytic bone lesions	BRx6, VRdx1, DVdx8 WM response- PR MM response- PR
3	75/M	IgMk	MM-50% WM-20%	ND	Negative	Retinal bleeding, anemia, GI bleeding, lymphadenopathy	VCdX1, BRx2 achieved VGPR DLBCL- R-CHOPx5 Died due to DLBCL
4	75/M	IgMk	WM- 50%	Normal	ND	Anemia	RCdX2, creatinine rose from 2 to 7 mg/dL, and renal biopsy demonstrated monoclonal plasma cells infiltrating the kidney. VCdX12 and light chain escape. Rd maintaining response for 7 years. MM response- VGPR
5	72/M	IgMk IgGk	WM- 50% With only a few focal clusters of plasma cells	Normal	Yes	Anemia	RCdX2 with minimal response and treatment changes to RVd WM response- PR
6	71/F	IgG-L IgM-K	MM 80% WM 10% (earlier 40%) PV related Fibrosis	t (4;14), Monosomy 13	Yes	Anemia and avid lytic bone lesions	Dara-RVd, followed by bortezomib/lenalidomide maintenance MM response- CR

VCd = bortezomib, cyclophosphamide dexamethasone; BR = bendamustine rituximab; VRD = bortezomib, lenalidomide, dexamethasone; DVd = daratumumab, bortezomib, dexamethasone; DRd = daratumumab, lenalidomide, dexamethasone; RCd = rituximab, cyclophosphamide and dexamethasone; Rd = lenalidomide and dexamethasone; Dara-RVd = Daratumumab, lenalidomide, bortezomib, dexamethasone, ND = Not done; PV = polycythemia vera.

Table 2. Previous case reports.

	Age/ gender	Paraprotein	Bone marrow biopsy	MYD 88 L265P	Organomegaly	Lytic lesions	Treatment
Case 1 Wang 2011	73/M	IgMk IgAk	MM 25% LPL 65%	NR	N	Y	Vd (once weekly), response deepening with the addition of lenalidomide, ASCT
Case 2 Mansour 2017	76/M	IgMk IgAk	MM 5-10% LPL (% NR)	Positive	N	Y	Bortezomib based regimen
Case 3 Fine 1981	73/F	IgMk-8.3 mg/mL IgGl-9.6 mg/mL	LPL-8% MM-3%	NR	Hepatomegaly lymphadenopathy	Y	First line: Radiation, vincristine, cyclophosphamide dexamethasone Relapsed after a month and second-line treatment was COP + doxorubicin
Case 4 Carulli 2013	75/F	IgMk IgGk		NR	N	Y	bortezomib, dexamethasone and rituximab
Case 5 McNutt 1973	54/M	IgM 1.2 IgG 7.2	75-85% plasma cells; Most of the remaining cells were small lymphocytes	NR	Hepatosplenomegaly	N	Melphalan, prednisone, and testosterone, plasmapheresis

multiple myeloma. Multiple myeloma is usually associated with IgG or IgA monoclonal proteins and only rarely (1%) IgM monoclonal proteinemia. We recommend using a diagnostic approach based on simultaneous use of clinical and laboratory data (i.e. morphology, flow cytometry, and molecular assays). Repeating the bone marrow biopsy at different time points can be helpful in identifying which disease is currently dominant and guide treatment decisions.

It is very important to differentiate between smoldering WM (SWM) and active Waldenström macroglobulinemia, since patients with SWM do not require

treatment for Waldenström macroglobulinemia. However, it is sometimes difficult to differentiate these two entities. Patients 1 and 6 were initially diagnosed as SWM that did not require treatment. When a SWM patient develops anemia, other causes of anemia should be ruled out before diagnosing a patient with symptomatic Waldenström macroglobulinemia and starting treatment. When the patient presents with anemia it can be difficult to determine the relative contributions of plasma cells and lymphoplasmacytic lymphoma. This is often done based on the percentage of infiltration in the bone marrow but often leads to therapy selection that is active in both entities including alkylating agents and proteasome inhibitors. The distinction is important now that therapies specific to plasma cells such as daratumumab and therapies specific to macroglobulinemia that are rituximab based or BTK based are available. The treating physician needs a high level of confidence in selecting therapy for the dominant clone responsible for illness.

Treatment of symptomatic Waldenström macroglobulinemia depends on the clinical presentation and includes rituximab, dexamethasone, chemotherapy, Bruton tyrosine kinase inhibitors (BTKi), bortezomib, and plasmapheresis in patients with symptoms suggestive of hyperviscosity [16]. The treatment of multiple myeloma includes proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, autologous stem cell transplantation, cyclophosphamide, bispecific antibodies, and CART [17]. Bortezomib and cyclophosphamide are well-established therapies for both entities. A Phase 1/2 in 17 relapsed Waldenström macroglobulinemia patients showed that lenalidomide is effective (ORR 29%) and safe at 15 mg/d [18]. The treatments used in our cohort were highly variable (Table 1). In multiple myeloma, we aim for a deep hematologic response while in Waldenström macroglobulinemia we aim for hemoglobin rise and symptom relief, not necessarily rapid and deep IgM reduction. Choosing a hybrid therapy to control both Waldenström macroglobulinemia and multiple myeloma is reasonable. However, we cannot infer the approach to the patient that does not meet the Waldenström macroglobulinemia and multiple myeloma response criteria. One patient in our cohort has died due to transformation to an intermediate lymphoma. All other patients are alive. This suggests that the simultaneous presentation of multiple myeloma and Waldenström macroglobulinemia may not be associated with a poor prognosis.

The main limitations of our case series are the number of patients and the retrospective nature of this cohort. Not all patients had data on MYD88 mutation. The treatment regimens were heterogeneous, and thus we cannot make general recommendations on treatment. Therefore, clinical deterioration should prompt further bone marrow, cytogenetic, and radiographic evaluation to identify the major and main leading disease process and treatment should be applied accordingly.

Conclusions

Concomitant multiple myeloma and Waldenström macroglobulinemia are rarely encountered and are not necessarily associated with biclonal protein. This entity poses a diagnostic challenge. Integrating the clinical, morphologic, immunophenotypic, cytogenetic, and mutational assays is necessary to correctly diagnose these patients and should guide the treatment approach.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

ORCID

Jorge J. Castillo http://orcid.org/0000-0001-9490-7532
Hamza Hassan http://orcid.org/0000-0003-1775-2703
Morie A. Gertz http://orcid.org/0000-0002-3853-5196

References

[1] Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the world health organization classification of haematolymphoid tumours: lymphoid neoplasms. Leukemia. 2022;36(7):1720–1748. doi:10.1038/s41375-022-01620-2

[2] Alley CL, Wang E, Dunphy CH, et al. Diagnostic and clinical considerations in concomitant bone marrow involvement by plasma cell myeloma and chronic lymphocytic leukemia/monoclonal B-cell lymphocytosis: a series of 15 cases and review of literature. Arch Pathol Lab Med. 2013;137(4):503–517. doi:10.5858/arpa.2011-0696-OA

[3] Hussein S, Gill K, Baer LN, et al. Practical diagnostic approaches to composite plasma cell neoplasm and low grade B-cell lymphoma/clonal infiltrates in the bone marrow. Hematol Oncol. 2015;33(1):31–41. doi:10.1002/hon.2129

[4] McMaster ML. The epidemiology of waldenström macroglobulinemia. Semin Hematol. 2023;60(2):65–72. doi:10.1053/j.seminhematol.2023.03.008

[5] Schop RF, Kuehl WM, Van Wier SA, et al. Waldenström macroglobulinemia neoplastic cells lack immunoglobulin heavy chain locus translocations but have frequent 6q deletions. Blood. 2002;100(8):2996–3001. doi:10.1182/blood.V100.8.2996

[6] Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in waldenström's macroglobulinemia. N Engl J Med. 2012;367(9):826–833. doi:10.1056/NEJMoa1200710

[7] Jiménez C, Sebastián E, Chillón MC, et al. MYD88 L265P is a marker highly characteristic of, but not restricted to, waldenström's macroglobulinemia. Leukemia. 2013;27(8):1722–1728. doi:10.1038/leu.2013.62

[8] Varettoni M, Arcaini L, Zibellini S, et al. Prevalence and clinical significance of the MYD88 (L265P) somatic mutation in waldenstrom's macroglobulinemia and related lymphoid neoplasms. Blood. 2013;121(13):2522–2528. doi:10.1182/blood-2012-09-457101

[9] Ngo VN, Young RM, Schmitz R, et al. Oncogenically active MYD88 mutations in human lymphoma. Nature. 2011;470(7332):115–119. doi:10.1038/nature09671

[10] Hanzis C, Ojha RP, Hunter Z, et al. Associated malignancies in patients with waldenström's macroglobulinemia and their kin. Clin Lymphoma Myeloma Leuk. 2011;11(1):88–92. doi:10.3816/CLML.2011.n.016

[11] Wang E, Kulbacki E, Stoecker M. Concomitant waldenstrom macroglobulinemia and IgA plasmablastic myeloma in a patient with untreated IgM paraproteinemia: sequential development of biclonal B-cell neoplasms over a 10-year period in a single individual. Hum Pathol. 2012;43(7):1135–1141. doi:10.1016/j.humpath.2011.11.001

[12] Mansour AT, Shandiz AE, Zimmerman MK, et al. Concomitant lymphoplasmacytic lymphoma and plasma cell myeloma, a diagnostic challenge. Am J Blood Res. 2017;7(2):10–17.

[13] Fine JM, Gorin NC, Gendre JP, et al. Simultaneous occurrence of clinical manifestations of myeloma and waldenström's macroglobulinemia with monoclonal IgG lambda and IgM kappa in a single patient. Acta Med Scand. 1981;209(3):229–234. doi:10.1111/j.0954-6820.1981.tb11582.x

[14] Carulli G, Ciancia EM, Azzarà A, et al. Simultaneous presentation of waldenström macroglobulinemia and multiple myeloma: multidisciplinary diagnosis, treatment and 30-month follow-up. J Clin Exp Hematop. 2013;53(1):29–36. doi:10.3960/jslrt.53.29

[15] McNutt DR, Fudenberg HH. IgG myeloma and waldenström macroglobulinemia. Coexistence and clinical manifestations in one patient. Arch Intern Med. 1973;131(5):731–736. doi:10.1001/archinte.1973.00320110115018

[16] Gertz MA. Waldenström macroglobulinemia: 2023 update on diagnosis, risk stratification, and management. Am J Hematol. 2023;98(2):348–358. doi:10.1002/ajh.26796

[17] Rajkumar SV. Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. Am J Hematol. 2022;97(8):1086–1107. doi:10.1002/ajh.26590

[18] Fouquet G, Guidez S, Petillon MO, et al. Lenalidomide is safe and active in waldenström macroglobulinemia. Am J Hematol. 2015;90(11):1055–1059. doi:10.1002/ajh.24175